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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/700,737	08/15/96	PONATH	LRS95-10

EXAMINER	
GAMBEL, P	
ART UNIT	PAPER NUMBER
1644	20

HM22/0716

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DATE MAILED: 07/16/99

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 3/15/99; 5/10/99

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-9, 11-45 is/are pending in the application.
Of the above, claim(s) 16-17, 21-22, 25-26, 29-40 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-9, 11-15, 23-24, 27-28 is/are rejected.
☐ Claim(s) 18-20 is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 17/18
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1998-404-496/40517

DETAILED ACTION

1. Applicant's amendment, filed 1/31/00 (Paper No. 24), is acknowledged. Claims 1, 8, 13, 18, 23, 24, 27 and 28 have been amended.

Claim 10 has been canceled previously.

Claims 16-17, 21-22, 25-26 and 29-45 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to nonelected inventions.

Claims 1-9, 11-15, 18-20, 23-24 and 27-28 are being acted upon presently.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action. This Office Action will be in response to applicant's arguments, filed 1/31/00 (Paper No. 24). The rejections of record can be found in previous Office Actions (Paper Nos. 7/12/20).

3. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the form PTO-948 previously sent in Paper No. 7.

4. Upon reconsideration of applicant's amended claims, filed 1/31/00 (Paper No. 24); the previous rejections under 35 U.S.C. § 112, second paragraph, have been obviated.

5. Upon reconsideration of applicant's amended claims and arguments, filed 1/31/00 (Paper No. 24); the previous rejection under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Bendig et al. (U.S. Patent No. 5,840,299; 1449) as it would apply to the instant claims has been obviated.

6. Claims 1-9, 11-15, 18-20, 23-24 and 27-28 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Queen et al. (U.S. Patent No. 5,530,101) in view of Lazarovits et al. (J. Immunol. 151: 6482-6489, 1993) and in further evidence by the Information for Contributors for this Volume of the Journal of Immunology essentially for the reasons of record set forth in Paper Nos. 7/12/20

It is noted that the rejection of record does apply to claim 11-15 and it appears that the lack of reciting these claims in the previous Office Action was an oversight. The examiner apologizes for any inconience to applicant in this matter.

Applicant's arguments, filed 1/31/00 (Paper No. 24), have been fully considered and are not found convincing essentially for the reasons of record.

Applicant argues in conjunction with In re LeGrice and Ex parte Thomson that there is insufficient evidence to create a presumption of public availability of the Act-1 hybridoma. Applicant also argues that the authors who publish in the Journal of Immunology are not obligated to make all materials referred to or described in a publication available or to make unique materials available for any purposes other than verification of published results. Applicant asserts that the presumption of public availability is improper.

However, the record is clear that the hybridoma was available to others. It is clear that Lazarovits et al. (J. Immunol. 151: 6482-6489, 1993)prepared the Act -1 antibody/hybridoma (see entire document, including page 6483, column 1, Patients and Methods, Antibodies). Applicant admits that the hybridoma was produced by Lazarovits in the laboratory of Colvin and that the assignee LeukoSite, Inc. obtained the Act-1 hybridoma through a licensing agreement with he General Hospital Corporation, employer of Drs. Lazarovits and Colvin at the time the Act-1 was made (see page 12 of applicant's amendment).

Applicant asserts that the record does not contain any evidence which indicates that the Act-1 hybridoma was made available to others or that the authors of the cited references were under any obligation to make the Act-1 hybridoma freely available to others at the time the invention was made.

However, Lazarovits and Karsh, authors of (J. Immunol. 151: 6482-6489, 1993) and Lazarovits and Colvin, by applicant's admission, appear to be the others or another. Another means other than applicants. Here, the Act-1 hybridoma was made and was available to another. Given that the rejection is based upon the obvious of CDR-grafted antibodies, given the availability of the particular hybridoma; the obviousness rejection is maintained.

Also, it is noted that applicant has not made of record the dates or conditions of obligations made by Lazarovits and Karsh (or Colvin) prior to applicant's filing date or at the time the invention was made.

Applicant's argues in conjunction with the Landau Declaration under 37 CFR § 1.132 that the claimed humanized antibodies possesses unexpected properties, including unexpected pharmacokinetic and phamacodynamic properties, which make them unobvious.

Applicant also argues in conjunction with Schwighoffer et al. J. Immunol. 151: 711-729, 1993) that there was insufficient expectation of success that the humanized Act-1 antibody could be used successfully as a therapeutic agent or that any advantage could be realized by producing a humanized Act-1.

Applicant also argues that the prior art does not disclose the CDR amino acids sequences in the claims.

The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 217 USPQ 1, 5 - 6 (Fed. Cir. 1983).

The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. Ex parte Obiaya , 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Applicant's reliance on unexpected results do not overcome clear and convincing evidence of obviousness. Also see Richardson-Vicks Inc. v. Upjohn Co., 44 USPQ2d 1181 (CAFC 1997)

The following is a reiteration of the rebuttal set forth in the previous Office Action (Paper No. 20) for applicant's convenience.

This proposition that the references failed to teach the structure of the claimed antibody precludes the teachings thereof from serving as evidence to establish a prima facie case of obviousness is contrary to a body of law which holds that a product may be described by the process of making it. As pointed in Ex parte Goldgaber, 41 USPQ2d 1173, 1176 (BPAI 1996), there is nothing intrinsically wrong in the application of methodology in the rejection product claims under 35 USC 103 depending on the particular facts of the case, the manner and context in which methodology applies and the overall logic of the rejection. Nor does Bell or Deuel issue a blanket prohibition against the application of methodology in rejecting product claimed defining DNA of cDNA. It is perfectly acceptable to consider the method by which a compound is made in evaluating the obviousness of the compound. In determining obviousness, it is appropriate to consider such matters as the manner of preparation of the composition vis-a-vis the prior art, the structural similarities as well as differences between the claimed composition and that of the prior art and the presence or absence of properties which would unobvious in view of the prior art. As noted in In re Cofer, 354, F.2d 664, 148 USPQ 268 (CCPA 1966), the particular structure or form of a chemical compound is an important consideration in determining obviousness under 35 USC 103; but it is not the only consideration.. A compound may well be defined or described by characteristics other than its chemical structure.

As set forth in the prior art rejection; the selection process for desired properties is critical in the isolation of an antibody of interest. Though those skilled in the art may be unaware of the exact chemical structure of an antibody (e.g. amino acid or nucleic acid sequence), they are aware that it is composed of established relatively unchanging array of nucleotides and amino acids which code for the particular immunoglobulin. Importantly, they are also aware that the art known immunoglobulin probes would have been able to isolate the targeted antibody or immunoglobulin of interest. For example, one does not need to determine the amino acid sequence of a rearranged V (variable) region before cloning, as evidenced by Queen et al.. Similarly, the instant application has relied upon heavy and light chain probes to identify and isolate the claimed antibody species. In fact, it appears that applicant has relied upon a commercial kit to clone Act-1 (for example, see Example 1 of the instant specification). No specific probes were required to isolate Act-1 at the time the invention was made, provided that one screened for the desired biological properties, which relied upon the isolation of desired antibodies having high affinity and complementarity with the $\alpha 4\beta 7$ specificity and therefore structure. Immunoglobulin gene structure and organization were well understood in the art at the time the claimed invention was made and that strategies for cloning the DNAs encoding immunoglobulin variable regions genes were well established in the art at the time the claimed invention was made, as were methods for the production of DNA constructs comprising expression vectors containing DNAs encoding immunoglobulin variable regions. The determination and manipulation of the amino acid and nucleic acid sequence is an outcome and mechanism of such engineering. The art known procedures of making humanized antibodies enable the ability of the ordinary artisan at the time the invention was made to derive a humanized antibody that binds to $\alpha 4\beta 7$ and encompasses the claimed limitations including "substantially the same", "competes with murine Act-1" or "derived from Act-1" including the specific structures claimed.

The rejections of record clearly set forth motivation and a reasonable expectation of success in deriving humanized α4β7-specific antibodies, including the Act-1 antibody. In addition, it was known in the prior art that humanized antibodies to antigens of interest could be useful in a variety of modalities, including therapy as well as diagnostics and assays (see Queen et al., particularly columns 18-20). Also, antigen-binding fragments were known and used at the time the invention was made for the same or similar modalities encompassing therapeutics, diagnostics and assays.

It is noted that the claimed invention appears drawn to CDR-grafted humanized antibodies and not to humanized antibodies that have a number of modifications not predicted or obvious in view of the prior art of CDR-grafted antibodies, known and practiced at the time the invention was made.

Again as pointed out previously and above with respect to humanizing Act-1 itself; applicant has not provided any objective evidence that the Act-1 antibody/hybridoma was not available to others at the time the invention was made. It is noted the inventive entity of the instant application does not recite the authors/investigators who made and used the Act-1 antibody as relied upon in the prior art of record (Lazarovits et al., J. Immunol. 151: 6482, 1993) nor the first reference citing the construction of the Act-1 antibody (Lazarovits et al. J. Immunol. 133: 857, 1984; cited as reference 32 of the prior art reference and on page 2 of the instant specification as well as reference #AS on the 1449). Also, it is noted that Information for Contributors to the Journal of Immunology are expected to provide unique materials to qualified investigators. Therefore, it appears that the Act-1 antibody/hybridoma was available to others at the time the invention was made.

Therefore, applicant's reliance upon claiming discrete sequences for the α4β7 /Act-1-specific humanized antibodies are met by the prior art teachings.

Therefore, the combined references provide motivation with an expectation of success in deriving humanized α4β7 /Act-1-specific antibodies. Therefore, from the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention was a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments are not persuasive and the rejection is maintained

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
April 3, 2000